DEPARTMENT OF THE NAVY
OFFICE OF THE CHIEF OF NAVAL OPERATIONS
2000 NAVY PENTAGON
WASHINGTON, D.C. 20350-2000

IN REPLY REFER TO
6200
Ser N093B/103-05
March 28, 2005

Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Ladies and Gentlemen:

SUBJECT: DOCKET NUMBER 1980N-0208, PROPOSED RULE AND PROPOSED ORDER: BACTERIAL VACCINES AND TOXOIDS

On behalf of Navy Medicine, I appreciate this opportunity to comment on Docket 1980N-0208. This comment pertains to section IV of the Proposed Rule and Proposed Order: Anthrax Vaccine Adsorbed – Proposed Order. Prompt FDA action on this regulatory process will greatly advance and strengthen the national program of medical countermeasures to the anthrax threat to the United States and its armed forces.

The focus of this comment is the proposed order's discussion concerning the safety of anthrax vaccine adsorbed (AVA). The proposed order includes some discussion on this subject (29 Fed. Reg. 78286) but does not take note of many of the studies that support the conclusion that AVA is safe for the prevention of anthrax disease. The Institute of Medicine (IOM) report (cited in footnote 4 of the proposed order) includes a thorough review of safety studies and data on AVA through issuance of a report in March 2002. The IOM report is summarized (on page 2 of the report) as follows:

> "After examining data from numerous case reports and especially epidemiologic studies, the committee also concluded that AVA is reasonably safe. Within hours or days following vaccination, it is fairly common for recipients to experience some local events (e.g., redness, itching, swelling, or tenderness at the injection site), while a smaller number of vaccine recipients experience some systemic events (e.g., fever and malaise). But these immediate reactions, and the rates at which they occur, are comparable to those observed with other vaccines regularly administered to adults. The committee found no evidence that vaccine recipients face an increased risk of experiencing life-threatening or permanently disabling adverse events immediately after receiving AVA, when compared with the general population. Nor did it find any convincing evidence that vaccine recipients face elevated risk of developing adverse health effects over the longer term, although data are limited in this regard (as they are with all vaccines)."

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This IOM summary is well supported by the scientific information available on AVA.

Over the years, a body of pseudo-scientific writings related to anthrax vaccine has accumulated on various Internet sites and in other media. To support the final phase of the FDA review, I have attached copies of peer-reviewed articles from recognized medical journals that illuminate the safety experience with AVA in recent years. I selected cohort studies published before and since the March 2002 IOM report. These cohort studies used a variety of scientific study designs. The article titles are summarized in Enclosure 1. Highlights/major points of several of the peer reviewed studies published after issuance of the IOM report include:

- Among all active-duty military personnel from 1998 to 2000 (4,106,512 person-years of experience), hospitalization and ambulatory visit rates were higher in the pre-immunization than the post-immunization cohort. (Reference E)
- Gulf War veterans who self-report anthrax vaccination also report lesser degrees of health, but when the analysis is limited to veterans with objective vaccination records the health differential almost disappears. (Reference F)
- Among 154,456 anthrax-vaccinated and 562,377 unvaccinated Army Soldiers followed for 4.25 years, disability evaluations rates did not differ significantly; this finding held for numerous subset analyses as well. (Reference R)

The Department of Defense (DoD) has compiled clinical experience with more than 5.2 million doses of anthrax vaccine administered to more than 1.3 million people since March 1998. DoD has consistently shared that experience with independent panels of civilian physicians and scientists, both FDA and CDC, and published the findings in peer-reviewed literature.

We are grateful for FDA's consistent reliance on objective, verifiable evidence as its standard for evaluating safety. Applying that standard to the accumulated body of scientific evidence clearly supports the proposed order's conclusion that AVA is safe for use in prevention of anthrax disease.

Sincerely,

D. D. WOOFTER
Rear Admiral
Deputy Director for Naval Medicine

Enclosure: 1. Bibliography

Copy to: U.S. Army Military Vaccine Agency

Reference: Docket Number 1980N-0208, Proposed Rule and Proposed Order: Bacterial Vaccines and Toxoids

Enclosure 1. Recent Peer-Reviewed Cohort Studies Published in Recognized Medical Journals that Describe Safety Experience with Anthrax Vaccine

A. Catherino WH, Levi A, Kao T-C, Leondires MP, McKeeby J, Segars JH. The anthrax vaccine does not affect semen parameters, embryo quality, or pregnancy outcome in couples with a vaccinated male military service member. *Fertility & Sterility* 2005;83:480-483.
http://www.vaccines.mil/documents/library/Catherino_Anthrax_Vaccine_2005.pdf

Conclusion: Among 254 anthrax-vaccinated and 791 unvaccinated servicemen, anthrax vaccine does not affect semen concentrations, embryo quality, or pregnancy outcome. For details, see article.

B. Gunzenhauser JD, Cook JE, Parker ME. Acute side effects of anthrax vaccine in ROTC cadets participating in advanced camp, Fort Lewis, 2000. *Medical Surveillance Monthly Report* 2001;7(5):9-11. http://amsa.army.mil/1MSMR/2001/v07_n05.pdf.

Conclusion: 25 cadets who inadvertently received a 1-ml dose of anthrax vaccine for their first dose reported comparable injection-site symptoms and systemic symptoms, compared to 48 cadets who received the proper 0.5-ml volume. All reactions to the vaccine were mild and self-limited. None affected cadet training. For details, see article.

C. Hoffman K, Costello C, Menich M, Grabenstein JD, Engler RJM. Using a structured medical note for determining the safety profile of anthrax vaccine for U.S. soldiers in Korea. *Vaccine* 2003:21:4399-4409.
http://www.anthrax.mil/documents/library/VaccineJournalVol%2021.pdf

Conclusion: Among 2,824 Army personnel in Korea, regardless of gender, almost all reported events were localized or minor, self-limited, and did not lead to impairment of work performance; 0.4% to 1.7% consulted a clinic for an event after vaccination. For details, see article.

D. Hunter D, Zoutman D, Whitehead J, Hutchings J. Health effects of anthrax vaccination in the Canadian Forces. *Military Medicine* 2004;169:833-838.
http://www.anthrax.mil/documents/library/anthraxvaccinestudy.pdf

Conclusion: Contrasting 403 anthrax-vaccinated Canadian Forces personnel deployed to the Persian Gulf with 445 unvaccinated personnel deployed to Kosovo, no evidence that anthrax vaccination resulted in an increase in adverse health events in the 8-month period after completion of deployment. No statistically significant differences between groups were seen in the percent change before and after vaccination in the number of chart entries for specific diagnoses and symptoms. Time trends showed no unexplained increases in the rate of diagnosis and symptoms in the vaccinated group after vaccination. For details, see article.

E. Lange JL, Lesikar SE, Brundage JF, Rubertone MV. Comprehensive systematic surveillance for adverse effects of anthrax vaccine adsorbed, US Armed Forces, 1998-2000. *Vaccine* 2003;21:1620-28. http://www.anthrax.mil/documents/library/science.pdf

Conclusion: Among all active-duty military personnel from 1998 to 2000 (4,106,512 person-years of experience), hospitalization and ambulatory visit rates were higher in the pre-immunization than the post-immunization cohort. For details, see article.

F. Mahan CM, Kang HK, Dalager NA, Heller JM. Anthrax vaccination and self-reported symptoms, functional status, and medical conditions in the National Health Survey of Gulf War Era Veterans and Their Families. *Annals of Epidemiology* 2004;14(2):81-8. http://www.annalsofepidemiology.org/article/PIIS1047279703001248/abstract

Conclusion: Gulf War veterans who self-report anthrax vaccination also report lesser degrees of health, but when the analysis is limited to veterans with objective vaccination records the health differential almost disappears. For details, see article.

G. Matyas GR, Rao M, Pittman PR, Burge R, Robbins IE, Wassef NM, Thivierge B, Alving CR. Detection of antibodies to squalene: III. Naturally occurring antibodies to squalene in humans and mice. *Journal of Immunologic Methods* 2004;286(Mar):47-67. http://www.anthrax.mil/media/pdf/Squalene3.pdf

Conclusion: The presence of anti-squalene antibodies using a validated test method did not statistically differ, when comparing 40 retired workers vaccinated while employed at Fort Detrick to 372 age-matched unvaccinated civilians from nearby Frederick, Maryland. For details, see article.

H. Peeler RN, Cluff LE, Trever RW. Hyper-immunization of man. *Bulletin of the Johns Hopkins Hospital* 1958;103:183-98.

I. Peeler RN, Kadull PJ, Cluff LE. Intensive immunization of man: Evaluation of possible adverse consequences. *Annals of Internal Medicine* 1965;63:44-57. http://www.anthrax.mil/media/pdf/Intensive.pdf

J. White CS III, Adler WH, McGann VG. Repeated immunization: Possible adverse effects: Reevaluation of human subjects at 25 years. *Annals of Internal Medicine* 1974;81:594-600. http://www.anthrax.mil/media/pdf/Repeated.pdf

Conclusion: Building on the experiences described in reference H and I, reference J describes 97 men who received 52 to 134 ml of vaccines (including anthrax vaccine) between 1944 and 1971. None developed unusual diseases or unexplained symptoms that could be attributed to the repeated doses of multiple vaccines. For details, see articles.

K. Pittman PR, Gibbs PH, Cannon TL, Friedlander AM. Anthrax vaccine: Short-term safety experience in humans. *Vaccine* 2001;20:972-8. http://www.vaccines.mil/documents/library/Vaccine%2020(5-6)%20972-8.pdf

Conclusion: Among 1,583 laboratory workers who received 10,722 doses of anthrax vaccine from 32 separate vaccine lots (273 receiving 10 or more doses, 46 receiving 20 or more doses), local and systemic events resolved without extended time lost from work, hospitalization or long-term effects. The most common injection-site reactions were erythema and/or induration (3.2%). Most people who reacted to a dose of anthrax vaccine received subsequent doses without problems. But people who reported an injection-site reaction were more likely to report a local reaction to a later dose. For details, see article.

L. Pittman PR, Hack D, Mangiafico J, Gibbs P, McKee KT Jr., Eitzen EM, Friedlander AM, Sjogren MH. Antibody response to a delayed booster dose of anthrax vaccine and botulinum toxoid. *Vaccine* 2002;20(May 15):2107-15. http://www.anthrax.mil/documents/library/Antibody_resp.pdf

Conclusion: Among 495 vaccinated Soldiers at Fort Bragg, no adverse event caused lost time from work or hospitalization and all reactions resolved without lasting consequences. For details, see article.

M. Pittman PR, Kim-Ahn G, Pifat DY, Coonan K, Gibbs P, Little S, Pace-Templeton JG, Myers R, Parker GW, Friedlander AM. Anthrax vaccine: Safety and immunogenicity of a dose-reduction, route comparison study in humans. *Vaccine* 2002(Jan 31);20:1412-20. http://www.anthrax.mil/documents/library/Immunogenicity.pdf

Conclusion: Among 173 vaccinees, adverse events at the injection site were less common when the intramuscular route is used to administer anthrax vaccine, compared to the subcutaneous route. For details, see article.

N. Pittman PR, Coonan KM, Gibbs PH, Scott HM, Cannon TL, McKee KT Jr. Long-term health effects of repeated exposure to multiple vaccines. *Vaccine* 2004;23:525-36. www.vaccines.mil/documents/library/Longtermhealtheffects.pdf

Conclusion: Comparing 155 retired laboratory workers from Fort Detrick (average age 69 years) who received a median of 154 vaccinations or skin tests (92% of whom received anthrax vaccination) to 265 community controls from central Maryland, intensive vaccination was not associated with an elevated risk of any disease or medical condition. For details, see article.

O. Rehme PA, Williams R, Grabenstein JD. Ambulatory medical visits among anthrax vaccinated and unvaccinated personnel after return from southwest Asia. *Military Medicine* 2002;167:205-10. http://www.anthrax.mil/documents/library/SWasia.pdf

Conclusion: Among 4,045 vaccinated US Air Force personnel and 1,132 unvaccinated USAF personnel deployed to Southwest Asia, there were no statistically

significant associations between anthrax vaccination and any ambulatory diagnosis evaluated. For details, see article.

P. Sever JL, Brenner AI, Gale AD, Lyle JM, Moulton LH, West DJ. Safety of anthrax vaccine: A review and evaluation of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiology & Drug Safety* 2004;13: 825-840. http://www.anthrax.mil/media/pdf/SeverArticle.pdf

Q. Sever JL, Brenner AI, Gale AD, Lyle JM, Moulton LH, West DJ. Safety of anthrax vaccine: A review by the Anthrax Vaccine Expert Committee (AVEC) of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiology & Drug Safety* 2002;11:189-202. http://www.anthrax.mil/media/pdf/AVEC_ms.pdf

Conclusion: Among 1,793 anthrax vaccine recipients described in 1,857 reports to the Vaccine Adverse Events Reporting System, no unexpected patterns of adverse events were detected. For details, see article.

R. Sulsky SI, Grabenstein JD, Delbos RG. Disability among U.S. Army personnel vaccinated against anthrax. *Journal of Occupational & Environmental Medicine* 2004;46:1065-1075. http://www.anthrax.mil/documents/library/Anthrax2004.pdf

Conclusion: Among 716,833 active-duty Army Soldiers (154,456 anthrax-vaccinated and 562,377 unvaccinated) over 4.25 years, rates of disability evaluations did not differ significantly; this finding held for numerous subset analyses as well. For details, see article.

S. Tierney BC, Martin SW, Franzke LH, Marano N, Reissman DB, Louchart RD, Goff JA, Rosenstein NE, Sever JL, McNeil MM; Centers for Disease Control and Prevention's Anthrax Vaccine and Antimicrobial Availability Program. Serious adverse events among participants in the Centers for Disease Control and Prevention's Anthrax Vaccine and Antimicrobial Availability Program for persons at risk for bioterrorism-related inhalational anthrax. *Clinical Infectious Diseases* 2003;37(Oct 1):905-11. http://www.journals.uchicago.edu/CID/journal/issues/v37n7/31092/31092.web.pdf

Conclusion: Among 199 people who received anthrax vaccine related to the anthrax-spore bioterror attacks of fall 2001, no serious adverse events were associated with anthrax vaccine. For details, see article.

T. Wasserman GM, Grabenstein JD, Pittman PR, Rubertone MV, Gibbs PP, Wang LZ, Golder LG. Analysis of adverse events after anthrax vaccination in US Army medical personnel. *Journal of Occupational & Environmental Medicine* 2003;45(Mar):222-33. http://www.anthrax.mil/documents/library/AnthraxVaccineEvaluation.pdf

Reference: Docket Number 1980N-0208, Proposed Rule and Proposed Order: Bacterial Vaccines and Toxoids

Conclusion: Among 601 anthrax-vaccinated healthcare workers, most adverse events after vaccination were mild and self-limited. The results for all systemic complaints did not substantially vary between the first four doses. For details, see article.

U. Wiesen AR, Littell CT. Relationship between prepregnancy anthrax vaccination and pregnancy and birth outcomes among US Army women. *JAMA* 2002;287(Mar 27):1556-60. http://jama.ama-assn.org/cgi/reprint/287/12/1556.pdf

Conclusion: Among 3,136 anthrax-vaccinated and 956 unvaccinated active-duty women at Fort Stewart or Hunter Army Air Field, rates of conception and healthy birth were the same for both groups. For details, see article.